Marked-up Copy of Amended Claims:

4. An isolated nucleic acid molecule consisting of a nucleotide sequence encoding a p450 protein selected from the group consisting of:

(a) a nucleotide sequence that encodes a protein comprising the amino acid sequence of SEQ ID NO:2;

(b) a nucleotide sequence [nucleic acid molecule] consisting of the nucleic acid sequence of SEQ ID No: 1; and

(c) a nucleotide sequence [nucleic acid molecule] consisting of the nucleic acid sequence of SEQ ID No: 3[; and

(d) a nucleotide sequence that is completely complementary to a nucleotide sequence of (a)-(c)].

REMARKS

Objections of drawings:

The examiner stated that the drawings must be submitted. Applicants hereby submit the changes shown in the figures wherein the correction filed on 5/8/01 has been approved and entered.

Objection to the Specification:

The title has been changed to "Isolated nucleic acid molecule encoding cytochrome p450."

Rejection under 35 USC §101/112:

At page 4 of the Office Action, the Examiner rejected the claims under 35 U.S.C.§101/112. In summary, the Examiner stated that the claimed invention is not supported by either a specific and substantial utility or a well-established utility. The Examiner stated that invention belongs to cytochrome p450 drug-metabolizing enzyme subfamily is a generic asserted utility. The Examiner pointed that the specification failed to disclose the function/activity of the protein consisting of SEQ ID NO: 2 or its relationship to any disease, and the specification does not show any enzyme assays demonstrating that the protein consisting of SEQ ID NO: 2 has cytochrome p450 enzymatic activity. The Examiner concludes that the main utility of the nucleic acids and protein is to carry out further research to identify the biological function and possible diseases associated with the nucleic acids and protein.

Applicants respectfully disagree with the Examiner.

Applicants would like to direct Examiner's attention to a recently discovered article authored by Rylander et al (Biochemical and Biophysical Research Communications 281, 529-535 (2001)).

In a sequence homology search, Applicants found SEQ ID NO: 2 of the instant invention shares a 100% sequence homology with the protein sequences studied in the above reference. Exhibition A discloses a sequence alignment of SEQ ID NO: 2 and the

sequence of Cytochrome P450 2S1 (CYP2S1) studied by Rylander et al (see attached Exhibition A).

Rylander et al disclosed a novel human cytochrome P450 2S1 (CYP2S1). The reference disclosed that CYP2S1 mRNA transcripts are expressed in lung, stomach, small intestine, and spleen. The expression is also relatively abundant in colon, appendix, liver, kidney, thymus, substantia nigra, peripheral leukocytes and placenta. The reference also disclosed a high level of expression in lung, small intestine and spleen and lower in colon, liver, kidney and peripheral leukocytes. Further study showed CYP2S1 located at ER by immunofluorescent microscopy. The reference finally suggested that CYP2S1 play a role in primary xenobiotic detoxification process, tissue-specific activation and human immune response.

As stated in the specification, the present invention is related to the Cytochrome 450 family 2 protein (see page 2 and 3 of Figure 2). The utility of the protein of the present invention is depicted on pages 4-7, specifically it catalyzes the oxidation and dehydrogenation of a number of endogenous and exogenous lipophilic compounds (page 4, third paragraph). CYP2 subfamily protein is also associated with the malignancies of the stomach, liver, kidney (see page 6, third paragraph). The protein of the present invention also shows an expression in lung tumor, colon and human leukocyte, which is consistent with the CYP2S1 disclosed in the reference. In view of the support from Rylander reference, the protein of the present invention does belong to Cytochrome 450 family, which involves in phase I drug-metabolizing enzyme.

Support for the functional classification of the protein of SEQ ID NO:2 as being a member of CYP2 subfamily protein can also be found in Figure 2. For example, the Blast alignment shows that SEQ ID NO:2 shares most of the functional domains with CYP2G1. In addition, Hmmer search results (pfam.wustl.edu) on page 3 of Figure 2 shows that SEQ ID NO: 2 of the present invention has statistically significant homology to Cytochrome P450 domains.

In summary, supported by references disclosed above, the present invention meets the requirement of a specific, substantial and credible utility that is imposed by the Utility Guideline under 35 USC §101 and §112, 1st paragraph.

Rejection under 35 USC §112, first paragraph:

Claim 13 is rejected under 35 U.S.C. 112, first paragraph for lack of the enablement. The Examiner stated that the predictability of which 20mer oligonucleotide probe will hybridize specifically and preferentially to a nucleic acid molecule that encodes a protein comprising the amino acid sequence of SEQ ID NO:2, the nucleotide sequence of SEQ ID NO:1, or the SEQ ID NO: 3 is extremely low, because the Examiner claims that 20 mer is not specific enough to identify the said sequences.

Applicants respectfully disagree.

Although a 20-mer from a sequence could result in a nonspecific hybridization, one of skilled in the art would know how to select a 20 mer that is unique to the nucleotide sequence claimed. One of the skilled in the art would search an oligonucleotide based on the references provided by the Examiner, for example, the amount of G+C content. Moreover, the reference provide by the Examiner specifically showed that "screening of mammalian cDNA or genomic DNA libraries should be carried out with degenerate pools of oligonucleotides 17-20 nucleotides in length (see lines 4-5 from the bottom, page 11.8, Sambrook et al., Molecular Cloning). Therefore, 20 mer is sufficient.

Claim 4, 8, 9, 24, 27-29 are rejected for failing to provide written description of the nucleotide sequence that is 5' and 3' of any nucleotide sequence that encodes a protein comprising the amino acid sequence of SEQ ID NO:2 or a full complement thereof. The Examiner further stated that the specification does not provide a written description of the amino acid sequence that is N-terminal and C-terminal of SEQ ID NO:2. The specification also fails to describe additional representative species of these nucleic acid molecules and polypeptides by any identifying structural characteristics or properties for which predictability of structures is apparent. The examiner suggested that amending the claims to recite that the isolated nucleic acid molecule encodes a protein having cytochrome p450 activity may overcome this rejection.

In response to examiner's rejection, Applicants have amended claims to read on a cytochrome p450 protein in claim 4, thus the rejection should be withdrawn.

Exibition A:

>CRA|61000062730124 /altid=gi|13449277 /def=ref|NP_085125.1|
(NM_030622) cytochrome P450, subfamily IIS, polypeptide
1; cytochrome P450 family member predicted from ESTs;
cytochrome P540, subfamily IIS, polypeptide 1 [Homo
sapiens] /org=Homo sapiens /taxon=9606 /div=PRI
/dataset=nraa /length=504
Length = 504

Score = 1023 bits (2615), Expect = 0.0
Identities = 504/504 (100%), Positives = 504/504 (100%)

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Query: 1   MEATGTWALLLALALLLLLTLALSGTRARGHLPPGPTPLPLLGNLLQLRPGALYSGLMRL
60

            MEATGTWALLLALALLLLLTLALSGTRARGHLPPGPTPLPLLGNLLQLRPGALYSGLMRL
Sbjct: 1    MEATGTWALLLALALLLLLTLALSGTRARGHLPPGPTPLPLLGNLLQLRPGALYSGLMRL
60

Query: 61  SKKYGPVFTIYLGPWRPVVVLVGQEAVREALGGQAEEFSGRGTVAMLEGTFDGHGVFFSN
120

            SKKYGPVFTIYLGPWRPVVVLVGQEAVREALGGQAEEFSGRGTVAMLEGTFDGHGVFFSN
Sbjct: 61  SKKYGPVFTIYLGPWRPVVVLVGQEAVREALGGQAEEFSGRGTVAMLEGTFDGHGVFFSN
120

Query: 121 GERWRQLRKFTMLALRDLGMGKREGEELIQAEARCLVETFQGTEGRPFDPSLLLAQATSN
180

            GERWRQLRKFTMLALRDLGMGKREGEELIQAEARCLVETFQGTEGRPFDPSLLLAQATSN
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180

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240

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300

            VSTLAAFTVRQVQQHQGNLDASGPARDLVDAFLLKMAQEEQNPGTEFTNKNMLMTVIYLL
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Sbjct: 301 FAGTMTVSTTVGYTLLLLMKYPHVQKWVREELNRELGAGQAPSLGDRTRLPYTDAVLHEA
360

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420

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Sbjct: 361 QRLLALVPMGIPRTLMRTTRFRGYTLPQGTEVFPLLGSILHDPNIFKHPEEFNPDRFLDA
420

Query: 421 DGRFRKHEAFLPFSLGKRVCLGEGLAKAELFLFFTTILQAFSLESPCPPDTLSLKPTVSG
480

            DGRFRKHEAFLPFSLGKRVCLGEGLAKAELFLFFTTILQAFSLESPCPPDTLSLKPTVSG
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480
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Query: 481 LFNIPPAFQLQVRPTDLHSTTQTR 504
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Sbjct: 481 LFNIPPAFQLQVRPTDLHSTTQTR 504
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